

Prevalence of Colorectal Cancer in Iron Deficiency Anemia with a Positive Result on Immunochemical Fecal Occult Blood

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ABSTRACT

Background/Aims: This study was carried out to reveal the relationships between iron deficiency anemia and the results of an immunochemical fecal occult blood test, iron deficiency anemia and colorectal cancer.

Materials and Methods: Seventeen thousand and six hundred sixty four asymptomatic individuals were subjects of this study. They gave samples for an immunochemical occult blood test, and colonoscopy was carried out during a medical check-up. The subjects were divided into two groups, according to the laboratory findings on iron deficiency anemia, and the positivity rate of an immunochemical occult blood test as well as the detection rate for colorectal cancer were compared in the two groups. In addition, the detection rate for colorectal cancer were determined in four groups stratified by both the results of occult blood test and the presence of iron deficiency anemia.

Results: The occult blood test was positive in 18.4% and 3.8% of subjects with and without iron deficiency anemia, and the detection rate for colorectal cancer was 2.7% and 0.4% in subjects with and without iron deficiency anemia, respectively, indicating a significant difference in the positivity rate ($P < 0.001$) as well as the detection rate ($P < 0.05$) between the two groups. The detection rate for colorectal cancer was highest in subjects with iron deficiency anemia with a positive occult blood test, respectively.

Conclusions: These results suggest that there are positive associations between iron deficiency anemia and the results of an immunochemical occult blood test, and between the patients with iron deficiency anemia and colorectal cancer, and that colonoscopy is necessary particularly in cases where the immunochemical occult blood test is positive and there is a finding of iron deficiency anemia.

Key words: Colonoscopy,Colorectal cancer, Immunochemical fecal occult blood test, Iron deficiency anemia

INTRODUCTION

It is estimated that iron deficiency anemia occurs in 3.5-5.3% of adult men and postmenopausal women (1), and the majority of iron deficiency anemia occurring in adult and postmenopausal women is believed to be the result of gastrointestinal tract blood loss. The incidence of gastrointestinal pathology in patients with iron deficiency anemia varies from study to study, 27-95% (1-5). In the Western countries, colorectal cancer is the most important cause of iron deficiency anemia secondary to gastrointestinal bleeding. It is estimated to be 4-13% of outpatients and 16% of inpatients (2,6,7).

Occult gastrointestinal blood loss may present as a positive result of fecal occult blood test, or as iron deficiency anemia with or without positive fecal occult blood. The primary test adopted in Western countries for colorectal cancer screening has been the guaiac-impregnated chemical test (8-10). In Japan, on the other hand, the immunochemical occult blood test has been accepted as the primary method for fecal occult blood testing (11-15) which has greater diagnostic validity for colorectal cancer than a chemical guaiac test (16-18).

Only limited information, however, is available on the relation among the patients with iron deficiency anemia, the results of immunochemical fecal occult blood test, and colorectal neoplastic conditions. For this reason, the author attempted to clarify the relation between iron deficiency anemia and colorectal cancer, and to reveal the association of iron deficiency anemia to the results of an immunochemical fecal occult blood test through a medical check-up based cross sectional study.

PATIENTS AND METHODS

Seventeen thousand and six hundred sixty four asymptomatic people aged over forty years who participated in a medical check-up for colorectal cancer served as subjects of this study. The four samples of two-consecutive days' stool from each subject were tested by an immunochemical fecal occult blood test, Iatro Hemcheck, without dietary or medicinal restriction according to the test principle before conducting colonoscopy. Fecal smears from subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received colonoscopic examination.

All the subjects were workers of several companies, and they were recommended to attend the medical check-up for colorectal cancer from their companies. The age of subjects was between 40 years and 60 years, and female-male ratio of the subjects was 1.2.

All the subjects were divided into two groups, according to the laboratory findings on iron deficiency anemia; and an intergroup comparison was made in terms of their positivity rate of an immunochemical fecal occult blood test as well as the detection rate for colorectal cancer. In addition, the detection rate for colorectal cancer were compared in four groups stratified by both the results of an immunochemical fecal occult blood test and the presence of iron deficiency anemia. Anemia was defined as a hemoglobin level less than 12.5 g per deciliter for men and less than 11.5 g for women, with serum ferritin level of less than 45 μ g per liter and serum iron level of less than 40 μ g per liter.

The principles and procedures of the immunochemical test (Iatro Hemcheck: a latex agglutination inhibition test) used in this study are outlined as follow. A small plastic tube containing buffer, sealed by a cap with a

collection stick is prepared for the collection of feces. Firstly, those being examined are asked to stick the tip of collection stick into the fecal sample several times, then to seal the cap. One drop of the fecal liquid in the plastic tube are put in well and mixed with anti-human-hemoglobin antibody attached to latex particles. Samples are classified as positive results when no agglutination occurred within 1.5 minutes after test procedure was completed and negative results when agglutination occurred. This test does not cause the prozone phenomenon. This immunochemical test procedure is not complicated, and also suitable for use in an office setting and may be performed in a physician's office or in a small hospital laboratory. The manufacture's price per slide or is about US\$3.64 (¥400).

Statistical analysis was performed by chi-square test, and a two-tailed p value of less than 0.05 was defined as statistically significant.

RESULTS

Among 17664 participants in a medical check-up for colorectal cancer, iron deficiency anemia were positive in 1132 subjects (6.4%) and the results of an immunochemical fecal occult blood test were positive in 832 subjects (4.7%), and colorectal cancer were detected in 96 subjects (0.5%)(Table 1).

In 1132 subjects of iron deficiency anemia group and in 16532 subjects of non-iron deficiency anemia group, positive cases of an immunochemical fecal occult blood test were 208 for iron deficiency anemia group and 924 for non-iron deficiency anemia group. Thus, the positivity rate of an immunochemical fecal occult blood test in these two groups was 18.4% and 3.8%, respectively, indicating a substantial significant difference between the

two groups ($p < 0.001$)(Table 2). Colorectal cancer was detected in 31 and 65 subjects in these two groups, respectively. The detection rate for colorectal cancer was 2.7% for iron deficiency anemia group and 0.4% for non-iron deficiency anemia group, and there was a substantial significant difference between these two groups ($p < 0.05$)(Table 3). Also, the detection rate for colorectal cancer was 13.0% for iron deficiency anemia with positive occult blood group, 0.4% for iron deficiency anemia with negative occult blood group, 8.3% for non-iron deficiency anemia with positive occult blood group, and 0.1% for non-iron deficiency anemia with negative occult blood group, and there were substantial significant differences between iron deficiency anemia with positive occult blood group and iron deficiency anemia with negative occult blood group ($p < 0.001$), and non-iron deficiency anemia with positive occult blood group ($p < 0.05$), and non-iron deficiency anemia with negative occult blood group ($p < 0.001$)(Table 4).

DISCUSSION

In this cross sectional study, the positivity rate of an immunochemical fecal occult blood test was 18.4% and 3.8% in subjects with and without iron deficiency anemia, and the detection rate for colorectal cancer was 2.7% and 0.4% in subjects with and without iron deficiency anemia. These data imply both the higher positivity rate of an immunochemical fecal occult blood test and the higher prevalence of colorectal cancer in the subjects with iron deficiency anemia, and indicate that there are positive relationships of iron deficiency anemia to the results of immunochemical fecal occult blood test as well as the detection rate for colorectal cancer, and that lower digestive tract should be

considered as a potential source of blood loss, especially when the immunochemical fecal occult blood test is positive and there is a finding of iron deficiency anemia.

However, the above findings should be interpreted with caution. Upper gastrointestinal tract pathology, such as stomach cancer, peptic ulcer, and erosive esophagitis may lead to a iron deficiency anemia and a positive result on fecal occult blood test (19-21). In addition, small intestine disorders should be considered as a potential source of bleeding in patients with iron deficiency anemia. Especially, celiac sprue can lead to malabsorption of iron as well as to occult bleeding (22,23).

On the basis of the above concept that both upper and lower gastrointestinal tract lesions can bleed and cause a positive result on fecal occult blood test, bidirectional endoscopic examinations have been used to evaluate the gastrointestinal tract in the patients with a positive result on guaiac-impregnated chemical occult blood test and in patients with iron deficiency anemia. Indeed, these patients may have the abnormalities of upper digestive tract. Several studies have documented the pathology of upper digestive tract in 25-41% of the patients with positive results on guaiac-impregnated chemical tests (21,24-26). Also, cross sectional studies have demonstrated prominent abnormalities of upper digestive tract consistent with blood loss in 41% of 381 patients with iron deficiency anemia (2,27-29).

Relation between the location of gastrointestinal bleeding and likelihood of a positive result on fecal occult blood test is considered as follows, from the viewpoint of intraluminal metabolism of hemoglobin. In upper digestive tract, hemoglobin is divided to form heme and globin by gastric pepsin proteases and

pancreatic proteases in proximal small intestine. Some intraluminal heme is reabsorbed in small intestine. A portion of heme that is not absorbed and is converted to porphyrins and iron through poorly understood mechanism has been termed "intestinal converted fraction" of heme. This fraction is not detected by guaiac-impregnated tests. Globin in upper digestive tract is digested by pepsin and pancreatic and intestinal proteases and is thus not detected by immunochemical tests (30).

In the separate articles (31,32), the author demonstrated that the immunochemical fecal occult blood test detected primarily colorectal bleeding, and that this immunochemical test was unsuitable for the diagnosis of the patients with upper digestive tract diseases. This finding substantiates the view that human hemoglobin derived from upper digestive tract pathology is degenerated in intestinal tract with the antigenicity lost and can not be detected by the immunochemical fecal occult blood tests, which use antibodies directed against human globin epitopes, and that immunochemical tests for human hemoglobin have a theoretical advantage over guaiac-impregnated chemical tests in terms of localizing bleeding to the colon and rectum with great sensitivity (30).

Clinical symptoms can be traced to either upper or lower digestive tract are associated with identification of lesions by esophagogastroduodenoscopy or colonoscopy. Accordingly, for iron deficient patients with site-specific symptoms, the initial examination should be directed toward those symptoms. However, for asymptomatic patients with iron deficiency anemia, colonoscopic examination should be carried out initially, particularly when the immunochemical fecal occult blood test is positive.

In this study, upper gastrointestinal tract endoscopy was not conducted due to the operational difficulties. Although synchronous lesions of upper and lower gastrointestinal lesions are reported to be rare (29), it would be more desirable to conduct esophagogastroduodenoscopy, in order to enhance the reliability of this study.

In conclusion, the results of this investigation indicate that there is a positive association between iron deficiency anemia and the results of immunochemical fecal occult blood test, and that a finding of iron deficiency anemia with a positive result on immunochemical fecal occult test is an important for the detection of colorectal cancer.

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Table 1. Results of a medical check-up for colorectal cancer

I. No. of subjects	17664
II. No. of subjects with iron deficiency anemia (II / I)	1132 (6.4%)
III. No. of subjects with positive occult blood test (III / I)	832 (4.7%)
IV. No. of detected colorectal cancer (IV / I)	96 (0.5%)

Table 2. Comparison of positivity rate of an immunochemical fecal occult blood test in subjects with and without iron deficiency anemia in a medical check-up for colorectal cancer

Iron deficiency anemia	Immunochemical fecal occult blood test		Total
	Positive (%)	Negative (%)	
Positive	208 (18.4)*	924 (81.6)	1132
Negative	624 (3.8)	15908 (96.2)	16532
Total	832 (4.7)	16832 (95.3)	17664

*P<0.001 for difference in positivity rate of fecal occult blood test between subjects with and without iron deficiency anemia.

Table 3. Comparison of detection rate for colorectal cancer in subjects with and without iron deficiency anemia in a medical check-up for colorectal cancer

Iron deficiency anemia	Colorectal cancer		Total
	Positive (%)	Negative (%)	
Positive	31 (2.7)*	1101 (97.3)	1132
Negative	65 (0.4)	16467 (99.6)	16532
Total	96 (0.5)	17568 (99.5)	17664

*P<0.05 for difference in detection rate for colorectal cancer between subjects with and without iron deficiency anemia.

Table 4. Comparison of detection rate for colorectal cancer among 4 groups stratified by the results of immunochemical fecal occult blood and the presence of iron deficiency anemia in a medical check-up for colorectal cancer

Colorectal cancer	Iron deficiency anemia			
	Positive (1132)		Negative (16532)	
	Fecal occult blood test		Fecal occult blood test	
	Positive (208)	Negative (924)	Positive (624)	Negative (15908)
Positive (%)	27 (13.0)*	4 (0.4)	52 (8.3)	13 (0.1)
Negative (%)	181 (87.0)	920 (99.6)	572 (91.7)	15895 (99.9)

* $P < 0.001$ for difference in detection rate for colorectal cancer between iron deficiency anemia with positive occult blood and iron deficiency anemia with negative occult blood, and between iron deficiency anemia with positive occult blood and non-iron deficiency anemia with negative occult blood.

* $P < 0.05$ for difference in detection rate for colorectal cancer between iron deficiency anemia with positive occult blood and non-iron deficiency anemia with positive occult blood.